REMARKS

In the above-referenced Office Action, the Examiner rejected claims 1-12, 14-16, and 18-21 and withdrew claims 13, 17, and 22-35 as being drawn to a non-elected invention.

This Response cancels claims 4-10, 12, 14-17, and 22-35 without prejudice to, or disclaimer of, the subject matter of these claims; amends claims 1-3, 11, and 18-21; and adds new claims 36-51. After entry of the foregoing amendments, claims 1-3, 11, 13, 18-21, and 36-51 (4 independent claims, 25 total claims) remain pending in the application. Reconsideration is respectfully requested.

Objections

The Examiner objects to the recitation in claim 2 of "the said two or more protein" and suggests that this should be replaced with "the two or more protein." Applicants have amended claim 2 in accordance with the Examiner's suggestion and, therefore, request that this objection be withdrawn.

The Examiner objects to claims 5-9, 10-13, 14, and 15-17 under 37 C.F.R. 1.75(c) as being in improper form because each depends upon another multiple dependent claim. The Examiner further objects to claim 11 and contends that the claim recites a non-elected invention. Since claims 5-9, 10, 12, 14, 15, and 16 are canceled herein and since claims 13 and 17 have been withdrawn from consideration, Applicants respectfully submit that the Examiner's objection as to these claims is rendered moot. Regarding claim 11, Applicants submit that the claim is amended herein so as to depend from a single claim (claim 1) and to recite subject matter of the elected invention. Accordingly, Applicants respectfully request that these objections be withdrawn.

Rejections under 35 U.S.C. § 112, ¶ 2

Claims 1-12, 14-16, and 18-21 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully traverse this rejection.

Regarding claims 1 and 3, the Examiner contends that the claims lack correlation between the preamble and the recited method steps. Applicants submit that claim 1 is amended herein such that the preamble and the body of the claim are consistent with each other. Specifically, claim 1 recites "at least one of two or more proteins" in the preamble and recites "two or more protein encoding regions" in the body of the claim. With respect to claim 3, Applicants are unclear as to why the Examiner believes that the preamble and the body of this claim are inconsistent with each other. Claim 3 recites "multiple proteins" in the preamble and recites "two or more protein encoding regions" in the body of the claim. The ordinary meaning of "multiple" is "more than one," which is entirely consistent with a recitation of "two or more." Applicants respectfully submit that claim 3 adequately apprises one of ordinary skill in the art of its scope and, therefore, satisfies the notice function required by 35 U.S.C. § 112, second paragraph.

Regarding claims 1 and 3, the Examiner further contends that recitation of the terms "isolatable" and "derived" render the claims indefinite. Applicants respectfully submit that claims 1 and 3 no longer recite these terms, thereby obviating the rejection.

Regarding claims 3 and 15, the Examiner indicates that the object of the phrase "a fragment thereof" is unclear. Applicants respectfully submit that claim 3 no longer recites the phrase "a fragment thereof" but recites, instead, "a fragment of said propeptide." Claim 15 is canceled herein, thereby rendering this rejection moot as to that claim.

Regarding the Examiner's various rejections relating to claims 6-8, 8 and 15, 9, and 14-16, Applicants respectfully submit that since these claims are canceled herein, these rejections are thereby rendered moot.

Regarding claims 18-19, the Examiner contends that the metes and bounds of a "protease processing site" are unclear. Claims 18 and 19 are amended herein to recite a "protease recognition site" rather than a "protease processing site." Support for this amendment is found in the specification at, *inter alia*, page 8, lines 17-19. Applicants respectfully submit that claims 18-19 adequately apprise one of ordinary skill in the art of their scope and, therefore, satisfy the notice function required by 35 U.S.C. § 112, second paragraph.

Regarding claim 19, the Examiner contends that a "subtilisin-like" protease processing site is unclear. Claim 19 is amended herein to recite "wherein said protease recognition site is terminated by two basic amino acid residues." Support for this amendment is found in the specification on page 8, lines 17-19. Applicants respectfully submit that claim 19 clearly defines the claimed subject matter.

Regarding claim 20, the Examiner contends that the term "derived" is indefinite, as it is unclear what is encompassed in the derived product. Claim 20 is amended herein to recite "wherein the signal sequence comprises a signal sequence from a plant defensin gene." Applicants respectfully submit that claim 20 clearly defines the claimed subject matter.

Regarding claim 21, the Examiner contends that the phrase "multiple proteins" lacks antecedent basis in claim 1. Applicants submit that claim 21 no longer recites the phrase "multiple proteins."

Accordingly, Applicants respectfully request the withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, ¶ 1

Claims 1-12, 14-16, and 18-21 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that the specification does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope with the claims. In particular, the Examiner contends that Applicants do not reasonably provide enablement for a method that employs any fragment and variant of a linker propeptide from a plant antimicrobial protein and/or a virus to improve the expression levels of multiple proteins. Applicants respectfully traverse this rejection.

Applicants submit that since claims 4-10, 12, and 14-16 are cancelled herein, this rejection is rendered moot as to these claims.

Applicants believe that the Office has not met its burden of establishing that the practice of the claimed invention would require undue experimentation. The Examiner is reminded that "[e]nablement is not precluded by the necessity for some experimentation

such as routine screening." *In re Wands*, 858 F.2d 731, 736-737 (Fed. Cir. 1988). In fact, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.* at 737 (internal citation omitted).

The Examiner contends that the specification does not disclose

> a method that employs a fragment and variants (as defined in the specification) of the disclosed and non-disclosed linker propeptides, wherein the fragment or the variant acts as a propeptide and provide [sic] suitable cleavage sites.

Office Action, p. 6. The Examiner further contends "Applicant has not provided guidance for modifications to the disclosed peptides that resulted [in] variants and fragments that retain propeptide activity." Office Action, p. 6.

Contrary to the position advanced by the Examiner, Applicants submit that the instant disclosure provides considerable guidance and direction regarding the linker propeptides that may be expressed in a plant in accordance with the claimed invention. For example, as described in the specification, beginning at p. 12, line 17 and continuing through p.13, line 7 (emphasis added),

> The Ib-AMP gene comprises five propeptide regions all of which are suitable for use in the present invention and which are described fully in Published International Patent Application WO 95/24486 at pages 29 and 40 to 42, the contents of which are incorporated herein by reference. All or part of the C-terminal propeptides derived from the Dm-AMP and Ac-AMP gene may be used.
>
> In a particularly preferred embodiment, the linker propeptide sequence used comprises a naturally occurring linker propeptide sequence which is modified so that amino acids from said sequence remaining attached to protein product after cleavage thereof is reduced, preferably so that none remain. Suitable modifications may be determined using routine methods as described herein. In its simplest form, protein products of the invention are isolated and analyzed to see whether they include any residual amino acids derived from the propeptide linker. The linker sequence may then be modified to eliminate some or all of these residues, provided the function of post-translational cleavage remains.
>
> ....

> Examples of linker propeptide sequences are SEQ ID NOs 3, 4, 6, 7, 21, 22, 23, 24, 25, 26, 27, 28 and 29 as shown herein and variants therefore which act as a propeptide.

In addition to the above-quoted descriptive guidance for suitably modifying a linker propeptide, the specification (Example 11) describes a number of constructs comprising various fragments of the fourth internal propeptide of the IbAMP precursor (*i.e.*, fragments of SEQ ID NO: 3).

Further, two references by François et al. demonstrate the accuracy of Applicants' statements in their specification. See *In re Marzocchi*, 439 F.2d 220, 223-24 and note 4 (C.C.P.A. 1971) (stating that pertinent references, which need not be prior art references, may be used to demonstrate the accuracy of a statement in a specification).

François et al., Plant Physiol. Biochem. 40: 871-879 (2002) (submitted with Supplemental IDS), demonstrates, *inter alia*, the following:

- Various fragments of the linker propeptide identified as SEQ ID NO: 3 in Applicants' specification can be used to enhance expression levels of at least one of two or more proteins linked by the fragment (see, *inter alia*, p. 872-73, Figure 1 (B))
- When fragments corresponding to Applicants' SEQ ID NOs: 21, 22, 23, and 29 were each used as a linker propeptide to form a polyprotein comprising DmAMP1 and a modified form of RsAFP2, the fragment significantly enhanced the expression level of DmAMP1 as compared to a single protein construct containing DmAMP1 (see p. 873, Table 1 and Figure 2)
- When a fragment corresponding to Applicants' SEQ ID NO: 22 was used as a linker propeptide to form a polyprotein comprising DmAMP1 and a modified form of RsAFP2, the fragment significantly enhanced the expression levels of both DmAMP1 and RsAFP2 as compared to single protein constructs containing either DmAMP1 or RsAFP2

François et al., Plant Physiol. 128: 1346-1358 (2002) (submitted with Supplemental IDS), demonstrates, *inter alia*, the following with respect to an expression cassette comprising a linker propeptide identified as SEQ ID NO: 3 in Applicants' specification (see, *inter alia*, p. 1348, Figure 1 (B)):

- Expression levels of both proteins linked by the propeptide can be enhanced relative to the expression levels produced by single-

protein constructs for each of the proteins (see, *inter alia*, pp. 1350-51, Table II and Figure 4).

- Both of the co-expressed proteins are primarily secreted extracellularly rather than being deposited intracellularly (see, *inter alia*, p. 1349).

The Examiner further contends,

> the working examples disclosed in the specification is [sic] limited to the expression of antimicrobial polyproteins separated by a linker propeptide from an antimicrobial protein. However, it is unclear whether the linker propeptide from the antimicrobial protein would also provide the same desired result with the non-antimicrobial polyprotein.

Office Action, p.7.

Applicants respectfully disagree with the Examiner. The instant specification provides considerable guidance and direction regarding the proteins that may be used in the practice of the claimed invention. For example, in addition to the antimicrobial proteins described in the working examples, the specification (pp. 15-16) describes a variety of other exemplary proteins that may be employed:

> Examples of proteins which may be expressed according to the methods of the present invention include, for example, antifungal proteins described in Published International Patent Application Nos W092/15691, W092/21699, W093/05153, W093/04586,W094/11511, W095/04754, W095/18229, W095/24486, W097/21814 and W097/21815 including Rs-AFP1, Rs-AFP2, Dm-AMP1, Dm-AMP2, Hs-AFP1, Ah-AMP1, Ct-AMP1, Ct-AMP2, Bn-AFP1, Bn-AFP2, Br-AFP1, Br-AFP2, Sa-AFPI, Sa-AFP2, Cb-AMP1, Cb-AMP2, Ca-AMP1, Bm-AMPl, Ace-AMPl, Ac-AMP1, Ac-AMP2, Mj-AMPl, Mj-AMP2, Ib-AMPl, Ib-AMP2, Ib-AMP3, Ib-AMP4, PR-1 type proteins such as chitinases, glucanases such as beta 1,3 and beta 1,6 glucanases, chitin-binding lectins, zeamatins, osmotins, thionins and ribosome-inactivating proteins and peptides derived therefrom ...

Applicants submit that the Examiner has not established a reasonable basis to question the enablement provided for this aspect of the claimed invention. In their natural state, each of the various propeptides of the IbAMP precursor separate one IbAMP antimicrobial peptide encoding region from another IbAMP antimicrobial peptide encoding region. While each of the IbAMP peptides are closely related to each other, these peptides

are unrelated to other antifungal and/or antimicrobial plant defense proteins. As described in Applicants' specification, a propeptide that separates two IbAMP proteins can also be used to mediate effective expression *in planta* of totally unrelated plant defense proteins, such as RsAFP1 and DmAMP1. Since there is no structural similarity between either RsAFP1 or DmAMP1 and any of the IbAMP peptides, there is no reason to believe that a propeptide of the IbAMP precursor could not be used to mediate efficient *in planta* expression of other structurally dissimilar proteins. Moreover, the prior art in the area of polyprotein expression implies that peptide linkers may be used outside of their natural context (see, *e.g.*, Specification, p. 2, lines 17-26) to effect the expression of two different enzymes. Therefore, Applicants respectfully submit that there is no reason to doubt that the claimed invention may be employed to express any desired protein in a plant.

Enclosed herewith is an unsigned Declaration of Jason Vincent under 37 C.F.R. § 1.132. Briefly, the Declaration describes experiments that demonstrate the use of a propeptide of an IbAMP precursor to mediate the efficient co-production in transgenic plant cells of a small (approx. 3.3 kDa) insecticidal peptide and a large (approx. 68 kDa) protein (β-glucuronidase). Applicants respectfully request that the Examiner consider the unsigned Declaration, pending Applicants' submission of a signed Declaration as soon as such can be obtained from the overseas declarant.

In view of the considerable direction and guidance provided by the specification, Applicants respectfully submit that the Examiner has failed to establish a reasonable basis to question the enablement provided for the claimed invention. Through both general teachings and more detailed examples, including the provision of exemplary proteins as well as exemplary fragments of disclosed linker propeptides and methods for determining how to obtain appropriate fragments, the specification enables one skilled in the art to practice the claimed invention throughout its entire scope. The practice of various disclosed embodiments of the claimed invention would have required no more than the routine preparation of vector constructs, in accordance with the teachings of the disclosure, and limited and systematic routine screening of, for example, plants transformed to express the various species of proteins and linker propeptides within the described classes of

proteins and linker propeptides. Applicants submit that, even where required, such efforts do not rise to the level of undue experimentation.

For the foregoing reasons, Applicants respectfully submit that the instant specification would have provided sufficient guidance to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation. Accordingly, the claimed invention is enabled, and Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, ¶ 1

Claims 4-12 and 14 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner contends that these claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Applicants respectfully submit that since claims 4-10 and 12 are cancelled herein, this rejection is rendered moot as to these claims.

Claim 11 recites, "The method according to claim 1, wherein said linker propeptide comprises an amino acid sequence of SEQ ID NO: 3 or fragments thereof."

Applicants submit that the instant specification adequately describes the claimed invention and clearly allows persons of ordinary skill in the art to recognize that Applicants invented the claimed subject matter. As stated in MPEP § 2163.II.A, "[t]he examiner has the initial burden ... of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims.". Mere conclusory statements cannot satisfy this burden.

Applicants believe that the Examiner has offered insufficient reasons as to why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. Specifically, the Examiner states,

> Applicant has not described all proteins and linker propeptides required by the claimed methods. Applicant only describes a method

> that employs two plant defensins, namely, DmAMP1 and AcAMP2. Applicant has not described other proteins and all variants and fragments of the linker propeptide as broadly claimed.

Office Action, p. 8.

However, contrary to the position advanced by the Examiner, § 112, first paragraph does not require a description of all proteins and linker propeptides encompassed by the claims. At most, the law requires a description of a representative number of species. Applicants submit that the instant specification satisfies the written description requirements of § 112, first paragraph. Not only does the specification provide sufficient teaching to clearly lead the skilled artisan to the relevant classes of proteins and linker propeptides to be expressed by a plant in accordance with the claimed invention, but it more than adequately describes a representative number of species within those classes.

For example, as detailed above with respect to the Examiner's enablement rejection, the specification teaches numerous proteins that can be employed in the practice of the claimed invention. See Specification, pp. 15-16. Additionally, the specification provides working examples that demonstrate the use of two particular proteins, Dm-AMP1 and Rs-AFP2. See, *e.g.*, Examples 2 and 4 and Table 1.

Moreover, the specification teaches several exemplary propeptides that can be used in the practice of the claimed invention, including, for example, an Ib-AMP propeptide having the amino acid sequence of SEQ ID NO: 3 and linker propeptides having amino acid sequences that are fragments of SEQ ID NO: 3. See also Specification, pp. 12-13, quoted above.

In addition, the specification provides examples that describe in detail, *inter alia*, the cloning of an exemplary protein encoding region (*i.e.*, Dm-AMP1) (see Example 1), the construction of various plant transformation vectors comprising various exemplary linker propeptides (*i.e.*, Ib-AMP, Dm-AMP1, and Ac-AMP2) (see Example 2), and modified constructs that each comprise a different fragment of an exemplary linker propeptide (*i.e.*, fragments of SEQ ID NO: 3) (see Example 11).

For the reasons set forth above, Applicants submit that the instant application provides sufficient written description support for the claimed invention. The law requires no more. Accordingly, Applicants respectfully request the withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 102(b)

Claims 1-12, 14-16, and 18-21 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Attenborough et al. (WO 95/24486, hereinafter "Attenborough"). Applicants respectfully traverse this rejection.

Applicants submit that since claims 4-10, 12, and 14-16 are cancelled herein, this rejection is rendered moot as to these claims.

Independent claim 1 recites: "at least one of said component protein molecules is expressed in said plant at a higher level than in a plant transformed with a DNA sequence encoding that component protein molecule alone." Applicants submit that Attenborough does not disclose or suggest this element. Thus, Attenborough does not disclose each and every element of claim 1 (and claims 2, 11, 18-21, and 36-38, each of which variously depends therefrom).

For the reasons set forth above with respect to claim 1, Applicants submit that Attenborough also does not disclose each and every element of claim 46 (and claims 47-49, each of which variously depends therefrom).

Independent claim 3 recites: "wherein said linker propeptide provides a cleavage site whereby an expressed polyprotein is post-translationally processed into its component protein molecules in a secretory pathway of said plant." Applicants submit that Attenborough does not disclose or suggest this element. Thus, Attenborough does not disclose each and every element of claim 3 (and claims 39-45, each of which variously depends therefrom) or claim 50 (and claims 51-53, each of which variously depends therefrom).

For the reasons set forth above with respect to claim 3, Applicants submit that Attenborough also does not disclose each and every element of claim 50 (and claims 51-53, each of which variously depends therefrom).

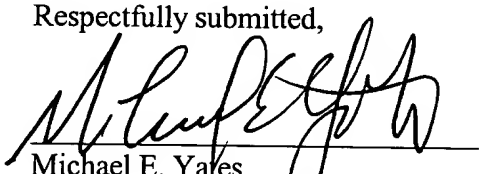
Accordingly, Attenborough does not anticipate the claimed invention, and Applicants therefore respectfully request the withdrawal of the rejection under 35 U.S.C. § 102(b).

CONCLUSION

Pursuant to the foregoing remarks, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. § 112 and are allowable over the prior art of record. No new matter is added by this amendment. Any and all amendments to the claims that are not specifically referenced in the above Remarks are intended to be cosmetic in nature and are not made for reasons related to the patentability of the claimed invention. Entry of the amendments is respectfully requested.

Reconsideration of the application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, the Examiner is invited to telephone the undersigned at the Examiner's convenience.

Respectfully submitted,



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